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1: Cancer Res. 2001 Mar 1;61(5):2301-6. Related Articles, Links

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EphA2 overexpression causes tumorigenesis of mammary epithelial cells.

Zelinski DP, Zantek ND, Stewart JC, Irizarry AR, Kinch MS.

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Elevated levels of protein tyrosine phosphorylation contribute to a malignant phenotype, although the tyrosine kinases that are responsible for this signaling remain largely unknown. Here we report increased levels of the EphA2 (ECK) protein tyrosine kinase in clinical specimens and cell models of breast cancer. We also show that EphA2 overexpression is sufficient to confer malignant transformation and tumorigenic potential on nontransformed (MCF-10A) mammary epithelial cells. The transforming capacity of EphA2 is related to the failure of EphA2 to interact with its cell-attached ligands. Interestingly, stimulation of EphA2 reverses the malignant growth and invasiveness of EphA2-transformed cells. Taken together, these results identify EphA2 as a powerful oncoprotein in breast cancer.

Publication Types:
- Research Support, Non-U.S. Gov't
- Research Support, U.S. Gov't, Non-P.H.S.
- Research Support, U.S. Gov't, P.H.S.

PMID: 11280802 [PubMed - indexed for MEDLINE]

2: Cancer Res. 2002 May 15;62(10):2840-7. Related Articles, Links

Full Text FREE Cancer Res

Antibody targeting of the EphA2 tyrosine kinase inhibits malignant cell behavior.

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EphA2 is a transmembrane receptor tyrosine kinase that is up-regulated on many aggressive carcinoma cells. Despite its overexpression, the EphA2 on malignant cells fails to bind its ligand, ephrinA1, which is anchored to the membrane of adjacent cells. Unlike other receptor kinases, EphA2 demonstrates kinase activity that is independent of ligand binding. However, ligand binding causes EphA2 to negatively regulate tumor cell growth and migration. Herein, we translate knowledge of EphA2 into strategies that selectively target malignant cells. Using a novel approach to preserve extracellular epitopes and optimize antibody diversity, we generated monoclonal antibodies that identify epitopes on the extracellular domain of EphA2. EphA2 antibodies were selected for their abilities to inhibit behaviors that are unique to metastatic cells while minimizing damage to nontransformed cells. A subset of EphA2 monoclonal antibodies were found to inhibit the soft agar colonization by MDA-MB-231 breast tumor cells but did not affect monolayer growth by nontransformed MCF-10A breast epithelial cells. These EphA2 antibodies also prevented tumor cells from forming tubular networks on reconstituted basement membranes, which is a sensitive indicator of metastatic character. Biochemical analyses showed that biologically active antibodies induced EphA2 phosphorylation and subsequent degradation. Antisense-based targeting of EphA2 similarly inhibited soft agar colonization, suggesting that the antibodies repress malignant behavior by down-regulating EphA2. These results suggest an opportunity for antibody-based targeting of the many cancers that overexpress EphA2. Our studies also emphasize how tumor-specific cellular behaviors can be exploited to identify and screen potential therapeutic targets.

Publication Types:
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- Research Support, U.S. Gov't, P.H.S.

PMID: 12019162 [PubMed - indexed for MEDLINE]

☐ **3:** J Cell Biochem. 2002;85(4):714-20. Related Articles, Links

Estrogen and Myc negatively regulate expression of the EphA2 tyrosine kinase.

Zelinski DP, Zantek ND, Walker-Daniels J, Peters MA, Taparowsky EJ, Kinch MS.

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Estrogen receptor and c-Myc are frequently overexpressed during breast cancer progression but are downregulated in many aggressive forms of the disease. High levels of the EphA2 tyrosine kinase are consistently found in the most aggressive breast cancer cells, and EphA2 overexpression can increase metastatic potential. We demonstrate, herein, that estrogen and Myc negatively regulate EphA2 expression in mammary epithelial cells. These data reveal EphA2 as a downstream target of estrogen

and Myc and suggest a mechanism by which estrogen and Myc may regulate breast cancer. Copyright 2002 Wiley-Liss, Inc.

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☐ **4:** J Biol Chem. 2002 Oct 18;277(42):39274-9. Epub 2002 Aug 6. Related Articles, Links

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Regulation of the EphA2 kinase by the low molecular weight tyrosine phosphatase induces transformation.

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Intracellular signaling by protein tyrosine phosphorylation is generally understood to govern many aspects of cellular behavior. The biological consequences of this signaling pathway are important because the levels of protein tyrosine phosphorylation are frequently elevated in cancer cells. In the classic paradigm, tyrosine kinases promote tumor cell growth, survival, and invasiveness, whereas tyrosine phosphatases negatively regulate these same behaviors. Here, we identify one particular tyrosine phosphatase, low molecular weight tyrosine phosphatase (LMW-PTP), which is frequently overexpressed in transformed cells. We also show that overexpression of LMW-PTP is sufficient to confer transformation upon non-transformed epithelial cells. Notably, we show that the EphA2 receptor tyrosine kinase is a prominent substrate for LMW-PTP and that the oncogenic activities of LMW-PTP result from altered EphA2 expression and function. These results suggest a role for LMW-PTP in transformation progression and link its oncogenic potential to EphA2.

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- Research Support, U.S. Gov't, P.H.S.

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☐ **5:** Mol Cancer Res. 2002 Nov;1(1):79-87. Related Articles, Links

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c-Cbl-dependent EphA2 protein degradation is induced by ligand binding.

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The EphA2 receptor protein tyrosine kinase is overexpressed and functionally altered in a large number of human carcinomas. Despite its elevated levels in cancer, the EphA2 on the surface of malignant cells demonstrates lower levels of ligand binding and tyrosine phosphorylation than the EphA2 on non-transformed epithelial cells. In our present study, we demonstrate that ligand-mediated stimulation causes EphA2 to be internalized and degraded. The mechanism of this response involves ligand-mediated autophosphorylation of EphA2, which promotes an association between EphA2 and the c-Cbl adaptor protein. We also show that c-Cbl promotes stimulation-dependent EphA2 degradation. These findings are important for understanding the causes of EphA2 overexpression in malignant cells and provide a foundation for investigating EphA2 as a potential target for therapeutic intervention.

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